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48. (New) The conjugate of claim 44, with the proviso that the tissue is not plasma.

REMARKS

Claims 41-48 have been added. No claims have been amended or canceled. With the entry of this amendment, claims 1-7, 9, 11, 17-18, 20-22 and 41-48 will be pending.

The Examiner rejected claims 1-7, 9, 11, 17-18 and 20-22 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed for at least the reasons set forth below.

The Examiner also variously rejected the claims over certain prior art. Claims 1-5, 11 and 20 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kobayashi et al. (Analytical Biochemistry 244: 374-383, Jan 1997; PTO 892) ("Kobayashi"). Claims 1-4 and 20 stand rejected under 35 U.S.C. 102(a) as being anticipated by U.S. Patent No. 4,292,250 issued to DeLuca et al. ("DeLuca"). Claims 6, 17 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi or DeLuca, each in view of U.S. Patent No. 5,576,309 issued to Tamara ("Tamara"). Finally, claims 21-22 were rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi or DeLuca, each in view of U.S. Patent No. 6,309,666 issued to Hatano ("Hatano"). All art-based rejections are respectfully traversed for at least the reasons given below.

The 112 Rejection

In paragraph 7 of the Office Action mailed May 9, 2001, the Examiner issued a § 112 rejection to claims 1-7, 9, 11, 17-18 and 20-22 that was virtually identical to the 112 rejection presently at issue. In response to this rejection, Applicants submitted the Declaration Under 37 C.F.R. 1.132 of Jeffrey W. Driscoll. Subsequently, in the Office Action issued December 4, 2001, the Examiner indicated that "[t]he enablement and the written description rejections of claims 1-7, 9, 11, 17-18, 20-22 under 35 U.S.C. 112 are hereby withdrawn in view of the declaration filed on 9/24/01 by Jeffrey W. Driscoll, Ph.D." Now, after Applicants have gone through the trouble and expense of filing a CPA to place the application in condition allowance

based on the Examiner and the Supervisory Examiner's recommendations, the Examiner has decided to reinstate the § 112 rejection.

In response to the reinstatement of this rejection, Applicants have resubmitted the Declaration of Jeffrey W. Driscoll, and respectfully encourage the Examiner to carefully review the contents thereof. Again, the gravaman of the Examiner's rejection appears to be that to one of ordinary skill in the art, Applicants' illustrated examples would fail to provide a representative number of species to describe the genus. All that is required, however, is that the application reasonably convey the claimed subject matter. In view of Dr. Driscoll's Declaration, Applicants respectfully submit that the description adequately supports the claims in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. One of ordinary skill in the art would easily be able to extrapolate and understand the scope of the claimed genus from the description and species provided in the specification. In view of Dr. Driscoll's Declaration, Applicants should not be limited to the disclosed species, as the scope of the claimed genus is fully supported by and could easily be determined from Applicants' specification and examples. "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation." MPEP § 2164.03.

Accordingly, reconsideration and withdrawal of the § 112 rejection are respectfully requested. The undersigned intends to contact the Examiner to further discuss this issue once the Examiner has had an opportunity to again review the Declaration. Alternatively, if the Examiner is prepared to discuss this issue, the Examiner is strongly encouraged to contact the undersigned by telephone to resolve this issue.

Rejection of Independent Claim 1 under § 102(a) and § 102(b)

The Examiner has rejected independent claim 1 and dependent claims 2-5 and 11 under 35 U.S.C. 102(a) as being anticipated by Kobayashi. The Examiner also rejected independent claim 1 and dependent claims 2-4 under 35 U.S.C. 102(b) as being anticipated by DeLuca.

Claim 1 recites "a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest." The gravaman of the Examiner's rejections appears to be that any biochemical moiety linked to a vitamin D moiety

anticipates the limitations of claim 1. Yet, Applicants have not claimed any conjugate with a vitamin D moiety. Applicants have claimed only those conjugates wherein a "target molecule" or "targeting molecules" as defined in the specification on page 9, lines 13-14 is linked to a vitamin D moiety. Neither Kobayashi nor DeLuca disclose or suggest such conjugates recited in claim 1.

Kobayashi "describes the generation of highly specific anti-1,25(OH)₂D₃ antibodies utilizing a novel immunogenic conjugate of 1,25(OH)₂D₃ with bovine serum albumin (BSA) linked through the C-11 α position." Kobayashi, col. 1, page 375. "The number of hapten molecules linked to a BSA molecule was calculated to be 17 from the uv absorption at 266 nm on the assumption that the molar extinction coefficient of the hapten is 16,600." *Id.* at col. 2, page 375. The production of the anti-1,25(OH)₂D₃ antibodies and their characterization follows:

Four domestic albino rabbits (female, 3 months old) were used for immunization. The solution of the hapten-BSA conjugate (1.2 mg) in isotonic saline (2 ml) was emulsified with complete Freund's adjuvant (2 ml), and a portion of the emulsion (approx 1 ml) was injected subcutaneously into each rabbit at multiple sites along the back . . . Blood was collected 9 days after the last immunization, and the immunoglobulin G (IgG) fraction was prepared from the resulting antiserum.

Id. at col. 2, page 374 to col. 1, page 375.

As indicated in Kobayashi's Results section, "four kinds of antisera against 1,25(OH)₂D₃ (As-1-As-4) were elicited by repeated immunization of four rabbits with the hapten 11 α -HG (Fig. 1) conjugated with BSA." *Id.* at col. 1, page 377. Figure 1 shows the "structure of 11 α -HG, a haptenic derivative of 1,25(OH)₂D₃ having a chemical bridge at the 11 α -position." *Id.* at col. 2, page 377.

Nevertheless, the Examiner contends that BSA is a target molecule moiety, and that BSA has an affinity for plasma. Although Kobayashi may disclose a "conjugate of 1,25(OH)₂D₃ with bovine serum albumin (BSA)," it does not teach or suggest that BSA is a "target molecule moiety" or that BSA can be used as a "target molecule moiety" as defined by the Applicants. Simply put, BSA is not a target molecule moiety. As described in Applicants' specification, the term "target molecule" or "targeting molecule" refers to "a molecule that binds to or influences metabolism of the tissue of interest." Applicants' specification, lines 13-14, page 9. As discussed in more detail below, BSA performs neither of these functions. In addition, Applicants

have provided the following examples to illustrate, but not limit, what is meant by a "target molecule moiety":

For example, bone-targeting agents may include bone-seeking molecules such as tetracycline, calcitonin, bisphosphonates, chelators, phosphates, polyaspartic acid, polyglutamic acid, aminophosphosugars, peptides known to be associated with mineral phase of bone such as osteonectin, bone sialoprotein and osteopontin, protein with bone mineral binding domains, and the like. Bone-targeting molecules may also include molecules which themselves affect bone resorption and bone formation rates, such as bisphosphonates, estrogens and other steroids, such as dehydroepiandrosterone (DHEA). These bone-seeking molecules may also possess bone growth therapeutic properties and/or result in a synergistic or additive effect with the vitamin D compound on bone resorption or formation. Skin-seeking molecules include certain metal ion-amino acid chelates; prostate-seeking molecules include certain steroids such as DHEA. Tumor-seeking agents include certain antibodies.

Applicants' specification, lines 14-27, page 9.

BSA simply does not fall within the scope of these examples or their equivalents, and again, does not bind to or influence metabolism of the tissue of interest.

In fact, Kobayashi does not teach or suggest that BSA has an affinity for any tissue of interest. The Examiner contends that BSA has an affinity for plasma, however, Applicants have studied Kobayashi and found no specific reference to BSA having an affinity for any tissue of interest. As a result, Applicants respectfully request that the Examiner direct Applicants' attention to a specific portion of Kobayashi in which BSA's affinity for plasma is specifically taught or suggested. BSA may be a constituent of bovine plasma, but there is no teaching or suggestion that by putting BSA on Kobayashi's 1,25(OH)₂ D₃ molecule, that the conjugate would somehow be directed toward or targeted to plasma. In contrast, Kobayashi's conjugate, namely the conjugate of 1,25(OH)₂ D₃ with BSA, is being used to produce anti-1,25(OH)₂ D₃ antibodies. In other words, Kobayashi's conjugate is being used as a target itself, rather than to target the 1,25(OH)₂ D₃ molecule to a tissue of interest. This is completely different from the claimed conjugate's "ability for site-specific targeting of vitamin D compounds using conjugates of vitamin D and a targeting molecule having an affinity for a tissue of interest." Applicants' specification, lines 3-5, page 9.

In summary, Kobayashi does not teach or suggest a target molecule moiety, nor does Kobayashi teach or suggest a target molecule moiety having an affinity for a tissue of interest. Accordingly, Kobayashi does not teach or suggest the subject matter of independent claim 1.

As to the DeLuca reference, DeLuca discloses "new 25-hydroxy vitamin D₂ 25-glucuronide derivatives among which is 25-hydroxy vitamin D₂ 25-D-glucuronic acid." DeLuca, abstract. "By virtue of the structural similarity of 25-hydroxy vitamin D₂ 25-D-glucuronic acid to 25-hydroxy vitamin D₂, a known biologically potent compound, the glucuronic acid compound should be a ready substitute for 25-hydroxy vitamin D₂ in various therapeutic applications and particularly where the water solubility of the glucuronic acid compound is a necessity or advantage." *Id.* "[T]he compound of this invention offers additional advantages in that it is water soluble." *Id.* at col. 1, lines 64-65. "Hence, it lends itself to intravenous and intramuscular dosage formulations and to administration to patients who have difficulty in assimilating lipids." *Id.* at col. 3, lines 65-68.

DeLuca does not teach or suggest the subject matter of independent claim 1. More particularly, DeLuca does not teach or suggest, among other things, a conjugate comprising a target molecule moiety having an affinity for a tissue of interest. The Examiner contends that glucuronide is a target molecule moiety, and that glucuronide has an affinity for plasma. First, while DeLuca may disclose "new 25-hydroxy vitamin D₂ 25-glucuronide derivatives among which is 25-hydroxy vitamin D₂ 25-D-glucuronic acid," it does not teach or suggest that glucuronide is a "target molecule moiety" or can be used as a "target molecule moiety" as defined by Applicants. Again, as described in Applicants' specification, the term "target molecule" or "targeting molecule" refers to "a molecule that binds to or influences metabolism of the tissue of interest." Applicants' specification, lines 13-14, page 9. As discussed in more detail below, glucuronide performs neither of these functions. In addition, glucuronide does not fall within the scope of the examples or equivalents thereof described in Applicants' specification, which is cited above. *See Applicants' specification*, lines 14-27, page 9. Simply put, glucuronide is not a target molecule moiety.

Nonetheless, the Examiner contends that glucuronide has an affinity for plasma. Applicants respectfully request that the Examiner direct Applicants' attention to a specific portion of DeLuca in which glucuronide's affinity for plasma is specifically taught or suggested. Applicants have studied DeLuca in detail, and found no specific mention or reference to plasma

or blood whatsoever in the patent. Consequently, DeLuca does not teach or suggest that 25-hydroxy vitamin D₂ 25-D-glucuronic acid would somehow be directed to or have an affinity plasma. DeLuca's vitamin D compound derivatives are simply not "characterized by an ability for site-specific targeting of vitamin D compounds using conjugates of vitamin D and a targeting molecule having an affinity for a tissue of interest." Applicants' specification, page 9, lines 3-5. Instead, DeLuca is directed to making vitamin D analogs and derivatives water-soluble. Generally, vitamin D analogs are not water soluble, and therefore, their application may be limited. By making these analogs water-soluble, "it lends itself to intravenous and intramuscular dosage formulations and to administration to patients who have difficulty in assimilating lipids." DeLuca, col. 3, lines 65-68. This, again, is much different than modifying the vitamin D so that it targets and has an affinity for a particular tissue of interest like Applicants' claimed invention.

In summary, DeLuca does not teach or suggest a target molecule moiety, nor does DeLuca teach or suggest a target molecule moiety having an affinity for a tissue of interest. Accordingly, DeLuca does not teach or suggest the subject matter of independent claim 1.

As a result, independent claim 1 and dependent claims 2-7, 9, 11 and 17-18 are allowable. Reconsideration and allowance of these claims are respectfully requested.

Rejection of Dependent Claim 7 under § 103(a)

Claim 7 depends from allowable claim 1, and is therefore allowable. In addition, claim 7 is further allowable because claim 7 contains additional patentable subject matter. More particularly, claim 7 recites the conjugate of claim 1, wherein the target molecule moiety is a bisphosphonate moiety.

The Examiner issued a 112 rejection against claim 7 as discussed above. Otherwise, no prior art rejections have been raised against claim 7. As a result, claim 7 is allowable because the 112 rejection has been addressed as discussed above. Accordingly, reconsideration and allowance of claim 7 are respectfully requested.

Rejection of Dependent Claim 9 under § 103(a)

Claim 9 depends from allowable claim 7, and is therefore allowable. In addition, claim 9 is further allowable because claim 9 contains additional patentable subject matter. More

particularly, claim 9 recites the conjugate of claim 7, wherein said bisphosphonate is linked to said vitamin D moiety at a position on the vitamin D moiety which is C-1, C-3, C-24 or C-25.

The Examiner issued a 112 rejection against claim 9 as discussed above. No prior art rejections have been raised against claim 9. As a result, claim 9 is allowable because the 112 rejection has been addressed as discussed above. Accordingly, reconsideration and allowance of claim 9 are respectfully requested.

Rejections of Independent Claim 20 under § 102(a) and § 102(b)

Independent claim 20 recites a pharmaceutical composition comprising a conjugate which includes at least one vitamin D moiety associated with at least one target molecule moiety having an affinity for a tissue of interest, and a suitable pharmaceutically acceptable carrier.

The Examiner rejected independent claim 20 under 102(a) as being anticipated by Kobayashi, or alternatively, under 102(b) as being anticipated by DeLuca.

Neither Kobayashi nor DeLuca teaches or suggests the subject matter of independent claim 20. More particularly, for the same and similar reasons as set forth above with respect to independent claim 1, neither Kobayashi nor DeLuca teaches or suggests a conjugate comprising a target molecule moiety having an affinity for a tissue of interest. Briefly, the Examiner contends that Kobayashi teaches BSA as a target molecule moiety, while DeLuca teaches glucuronide as a target molecule moiety. Because neither of these fall within Applicants' definition and examples of a target molecule moiety as discussed in more detail above, neither BSA nor glucuronide constitutes a target molecule moiety. Second, for the reasons set forth above, there is no teaching or suggestion in these references that BSA or glucuronide has an affinity for a tissue of interest. Accordingly, independent claim 20 is allowable.

In addition, neither Kobayashi nor DeLuca teaches or suggests a pharmaceutical composition comprising a pharmaceutically acceptable carrier. Applicants have defined "pharmaceutically acceptable carrier" as follows:

Suitable pharmaceutically acceptable carriers for use in the composition or method of the present invention include, but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils (e.g., corn oil, cottonseed oil, peanut oil, olive oil, coconut oil), fish liver oils, oily esters such as Polysorbate 80, polyethylene glycols, gelatine, carbohydrates (e.g., lactose, amylose or starch), talc, silicic acid, viscous paraffin, fatty acid

monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc.

Regarding Kobayashi, the Examiner contends that "the reference teaches the reference conjugate in isotonic saline for injection, which is a suitable pharmaceutically acceptable carrier." The Examiner, however, has overlooked the fact that the "solution of the hapten-BSA conjugate (1.2 mg) in isotonic saline (2 ml) was emulsified with complete Freund's adjuvant (2 ml), and a portion of the emulsion (approx 1 ml) was injected subcutaneously into each rabbit " Kobayashi, col. 2, page 375. To one of ordinary skill in the art, the term adjuvant means the following: "an additive to a vaccine [used] in order to stimulate or potentiate the immune response. In experimental animals, Freund's adjuvant is often used. In humans, this is not allowed and as adjuvant BCG is often used." *Some Terms in Parasitology*, www.icp.ucl.ac.uk/~opperd/parasites/terms.htm, July 8, 2002 (copy enclosed). Because it is well-understood in the art that a pharmaceutical composition comprising Freund's adjuvant is "not allowed," i.e. it is not suitable pharmaceutically in humans, Kobayashi would not be construed by one of ordinary skill in the art to teach a pharmaceutical composition comprising a suitable pharmaceutically acceptable carrier.

Regarding DeLuca, the Examiner has not cited any particular substance in DeLuca that could be construed as a suitable pharmaceutically acceptable carrier in light of Applicants' specification. In addition, the Examiner has provided no specific example and no rationale for why DeLuca would teach or suggest a suitable pharmaceutically acceptable carrier to one of ordinary skill in the art. Instead, the Examiner makes the conclusory statement that the reference anticipates the claimed invention. The Examiner is reminded of the Federal Circuit's recent *In re Zurko* decision in which it stated the following: "Conclusory statements such as those here provided do not fulfill the agency's obligation The board must set forth the rationale on which it relies." *In re Zurko*, 258 F.3d 1379, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). Applicants respectfully request that the Examiner identify the suitable pharmaceutically acceptable carrier in DeLuca that anticipates the invention. In view of the Examiner's failure to provide any specific citation to DeLuca, and further in view of the Examiner's failure to provide any rationale for this rejection, claim 20 is considered allowable.

Accordingly, reconsideration and allowance of claim 20 are respectfully requested.

New Dependent Claim 41

Claim 41 depends from allowable claim 1, and is therefore allowable. In addition, claim 41 is further allowable because claim 41 contains additional patentable subject matter. More particularly, claim 41 recites the conjugate of claim 1, with the proviso that the tissue is not plasma.

The Examiner contends that both Kobayashi and DeLuca teach plasma as a tissue of interest. Accordingly, explicitly removing plasma from the scope of "tissue" in claim 1 certainly lends patentability to claim 41. As a result, consideration and allowance of claim 41 are respectfully requested.

New Dependent Claim 42

Claim 42 depends from allowable claim 1, and is therefore allowable. Claim 42 is further allowable because claim 42 contains additional patentable subject matter. More particularly, claim 42 specifies the conjugate of claim 1, wherein the conjugate includes 1α -(OH)-24-aminoalkyl-1,1-bisphosphonate- D_2 , 1-aminoalkyl-1,1-bisphosphonate-24-(OH)- D_2 , 1α ,24-(OH) $_2$ -3-aminoalkyl-1,1-bisphosphonate- D_2 , 1α -aminoalkyl-1,1-bisphosphonate-25-(OH)- D_3 , 1α ,25-(OH) $_2$ -3-aminoalkyl-1,1-bisphosphonate- D_3 , 1α -(OH)-25-aminoalkyl-1,1-bisphosphonate- D_3 , and combinations thereof. This amendment is supported and enabled by pages 26-34 of Applicants' specification.

Because neither Kobayashi nor DeLuca teaches or suggests any of these specific conjugates, claim 42 is allowable. Consideration and allowance of claim 42 are respectfully requested.

New Dependent Claim 43

New claim 43 depends from allowable claim 20, and is therefore allowable. Claim 43 is further allowable because it contains additional patentable subject matter. More particularly, claim 43 recites the conjugate of claim 20, with the proviso that the tissue is not plasma.

For the same and similar reasons as set forth with respect to claim 41, claim 43 is allowable. Accordingly, consideration and allowance of claim 43 are respectfully requested.

New Independent Claim 44

New claim 44 recites a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest. The target molecule moiety includes at least one of tetracycline, calcitonin, a bisphosphonate, a phosphate, polyaspartic acid, polyglutamic acid, an aminophosphosugar, osteonectin, bone sialoprotein and osteopontin, protein with bone mineral binding domains, estrogen, a steroid, dehydroepiandrosterone (DHEA), a metal ion-amino acid chelate, an antibody and combinations thereof.

The Examiner contends that Kobayashi teaches a target molecule moiety, namely, BSA, and that DeLuca also teaches a target molecule moiety, namely, glucuronide. For the same and similar reasons as set forth above with respect to claim 1, neither Kobayashi nor DeLuca teach or suggest a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest. However, even assuming arguendo that BSA and glucuronide are target molecule moieties, neither Kobayashi nor DeLuca teach or suggest any of the target molecule moieties specifically listed in new claim 44.

Accordingly, consideration and allowance of claim 44 are respectfully requested.

New Dependent Claim 45

Claim 45 depends from allowable claim 44, and is therefore allowable. Claim 45 is further allowable because claim 45 contains additional patentable subject matter. More particularly, claim 45 specifies the conjugate of claim 44, wherein the conjugate includes 1α -(OH)-24-aminoalkyl-1,1-bisphosphonate- D_2 , 1-aminoalkyl-1,1-bisphosphonate-24-(OH)- D_2 , 1α ,24-(OH) $_2$ -3-aminoalkyl-1,1-bisphosphonate- D_2 , 1α -aminoalkyl-1,1-bisphosphonate-25-(OH)- D_3 , 1α ,25-(OH) $_2$ -3-aminoalkyl-1,1-bisphosphonate- D_3 , 1α -(OH)-25-aminoalkyl-1,1-bisphosphonate- D_3 , and combinations thereof.

Because neither Kobayashi nor DeLuca teaches or suggests any of these specific conjugates, claim 45 is allowable. Consideration and allowance of claim 45 are respectfully requested.

New Dependent Claim 46

Claim 46 depends from allowable claim 44, and is therefore allowable. In addition, claim 46 is further allowable because claim 46 contains additional patentable subject matter. More particularly, claim 46 recites the conjugate of claim 44, wherein the target molecule moiety is a bisphosphonate moiety.

For the same and similar reasons as set forth above with respect to claim 7, claim 46 is allowable. Accordingly, consideration and allowance of claim 46 are respectfully requested.

New Dependent Claim 47

Claim 47 depends from allowable claim 46, and is therefore allowable. In addition, claim 47 is further allowable because claim 47 contains additional patentable subject matter. More particularly, claim 47 recites the conjugate of claim 46, wherein said bisphosphonate is linked to said vitamin D moiety at a position on the vitamin D moiety which is C-1, C-3, C-24 or C-25.

For the same and similar reasons as set forth above with respect to claim 9, claim 47 is allowable. Accordingly, consideration and allowance of claim 47 are respectfully requested.

New Dependent Claim 48

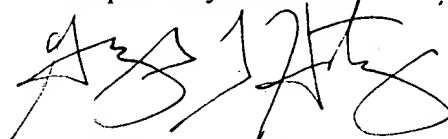
New claim 48 depends from allowable claim 44, and is therefore allowable. Claim 48 is further allowable because it contains additional patentable subject matter. More particularly, claim 48 recites the conjugate of claim 44, with the proviso that the tissue is not plasma.

For the same and similar reasons as set forth with respect to claim 41, claim 48 is allowable. Accordingly, consideration and allowance of claim 48 are respectfully requested.

CONCLUSION

In view of the foregoing, reconsideration and allowance of claims 1-7, 9, 11, 17-18 and 20-22, as well as consideration and allowance of claims 41-48 are respectfully requested. Applicants again wish to request a telephonic interview with the Examiner. The Examiner is strongly encouraged to contact the undersigned by phone should any issues remain.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'GJ Hartwig', written over a horizontal line.

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